CYCLOADDITION OF NITRILE IMINES AND DIELS-ALDER REACTION OF ANTHRACENE TO ISOXAZOLYL MALEIMIDES

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Abstract: The reaction of nitrile imines greated in situ from the arylhydrazones in the presence of chloramine-T with isoxazolyl maleimides **2** results isoxazolyl pyrrolo [3,4-*d*]-7.8-dihydro pyrazoles **3**. The dienophile **2**, anthracene and anhydrous aluminium chloride in dichloromethane at room temperature yielded, Diels-Alder adducts i.e., 9-10-dihydro-anthranene-9,10-*endo*-*N*-isoxazolyl maliemides 4. All the new products have been characterized by elemental analyses, IR, ^{1}H NMR and mass spectra data.

Introduction

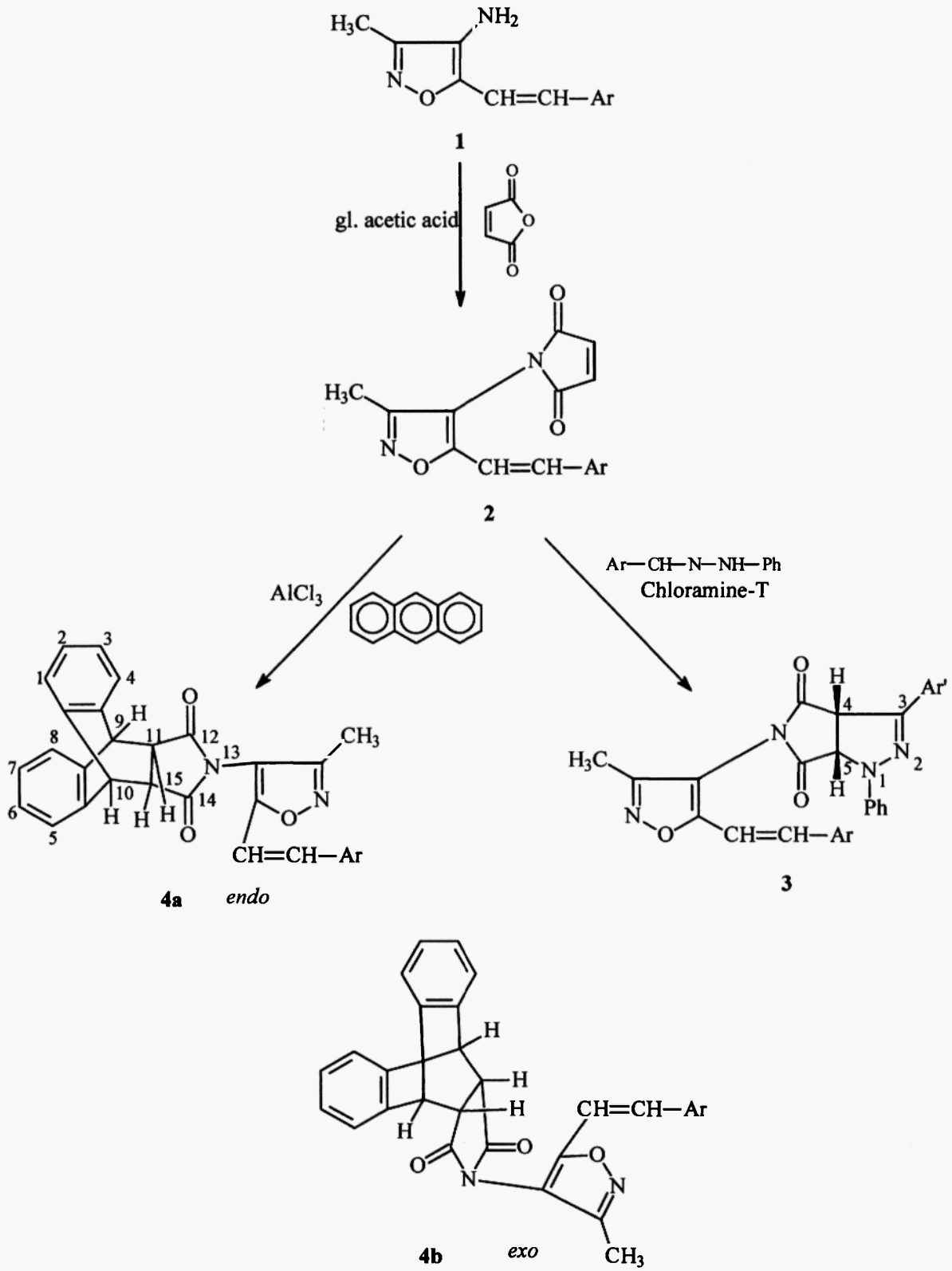
1,3-Dipolar cycloaddition using nitrile imines is a very well known process (1). These synthons (2) are often generated in situ from hydrazonyl chlorides and trapped with dipolarophiles to give the corresponding Δ^2-pyrazolines (3). Δ^2-pyrazolines are of interest due to their biological activity (4,5) and physical applications (6,7). Maleimide compounds are an important class of substrates for biological and chemical applications (8). In synthetic organic chemistry the maleimide functionality can be used as a synthetic platform in total synthesis due to its Michael-accepting ability and dienophilic nature (9-11). These is a scanty of information available in the literature, involving the synthesis of maleimide cycloaddition via 1,3-dipolar cycloadditions and Diels-Alder reaction. Recently, we have reported the cycloaddition of nitrile oxides to isoxazole maleimide compounds (12,13). As a sequel to our work an isoxazole maleimides, we present here our results in the reaction of isoxazole maleimides with nitrile imines and anthracene.

Results & Discussions

The reaction of 4-amino-3-methyl-5-styryl isoxazole **1** with maleic anhydride in glacial acetic acid resulted in the formation of *N*-(3-methyl-5-styryl-4-isoxazolyl)-maleimides **2** in quantitative yields (12). The cycloaddition reaction of nitrile imines, generated in situ from arylhydrazone by treatment with chloramine-T, with *N*-(3-methyl-5-styryl-4-isoxazolyl)-maleimides **2** has been carried out by refluxing in ethanol for 4 hrs. The product of cycloaddition reaction was identified as 3-aryl-1-phenyl-5-*N*-(3-methyl-5-styryl-4-isoxazolyl)-4,6-dioxopyrrolo-[3,4-*d*]-7,8-dihydropyrazoles **3** (Schemes and Table-1).

Similarly, Diels-Alder reaction was carried out between diene anthracene and dienophile *N*-(3-methyl-5-styryl-4-isoxazolyl)-maleimide **2** in presence of anhydrous aluminium chloride in dichloromethane at room temperature. The reaction resulted in 9,10-dihydro-anthracene-9,10-*endo*-*N*-(3-methyl-5-styryl-4-isoxazolyl)-maleimides 4 in good yields (Scheme and Table-1).

The structures of **3** and 4 are assigned on the basis of their elemental analyses and spectral data. The ^{1}H NMR specta (δ ppm) of **3** showed two distinct doublets at 4.5 and 4.7 due to C_4-*H* and C_5-*H* protons of pyrazole ring. The coupling constants (J = 5.0 Hz) values for these protons indicated that they are in *cis* orientation. Nitrile imine cyclo-addition to a double bond is a concerted reaction, hence these two bridge head hydrogens (sp^3) are in *cis* position, as they are in *cis* orientation in its precursor. The styryl double bond on isoxazole did not involve in the reaction with nitrile imines, as there is no change in the proton signals of styryl protons in the ^{1}H NMR of **3**, which is similar to its precursor **2**.


H3C
NH2
N
O
CH=CH—Ar
1
gl. acetic acid
O
O
O
H3C
N
O
CH=CH—Ar
2
AlCl3
Ar—CH—N—NH—Ph
Chloramine-T
CH3
CH=CH—Ar
4a endo
H3C
Ar'
Ph
CH=CH—Ar
3
H
H
H
H
CH=CH—Ar
CH3
4b exo

Scheme-1

Table-1: Physical data of compounds 3 and 4.

Entry	Ar	Ar'	m.p. (°C)	Yield (%)	Molecular formula	Found (Calcd) %		
						C	H	N
3a	C_6H_5	C_6H_5	176	55	$C_{29}H_{22}N_4O_3$	73.3	4.6	11.7
						(73.4	4.6	11.8)
3b	C_6H_4-Cl(*p*)	C_6H_5	182	50	$C_{29}H_{21}N_4O_3Cl$	68.3	4.0	11.1
						(68.4	4.1	11.0)
3c	C_6H_4-Cl(*o*)	C_6H_5	189	45	$C_{29}H_{21}N_4O_3Cl$	68.4	4.2	11.0
						(68.4	4.1	11.0)
3d	C_6H_4-OCH_3(*p*)	C_6H_5	186	55	$C_{20}H_{24}N_4O_4$	71.6	4.8	11.2
						(71.4	4.7	11.1)
3e	C_6H_4-CH_3(*p*)	C_6H_5	191	60	$C_{20}H_{24}N_4O_3$	73.6	4.9	11.5
						(73.7	4.9	11.4)
3f	C_6H_5	C_6H_4-Cl(*p*)	196	50	$C_{29}H_{21}N_4O_3Cl$	68.2	4.0	11.1
						(68.4	4.1	11.0)
3g	C_6H_5	C_6H_4-Cl(*o*)	205	45	$C_{29}H_{21}N_4O_3Cl$	68.3	4.2	11.0
						(68.4	4.1	10.9)
3h	C_6H_5	C_6H_4-NO_2(*p*)	216	50	$C_{29}H_{21}N_5O_5$	67.1	3.9	13.3
						(67.0	4.0	13.4)
3i	C_6H_4-Cl(*p*)	C_6H_4-Cl(*p*)	224	50	$C_{29}H_{20}N_4O_3Cl_2$	63.9	3.6	10.2
						(64.0	3.7	10.3)
3j	C_6H_4-CH_3(*p*)	C_6H_4-Cl(*p*)	210	55	$C_{30}H_{23}N_4O_3Cl$	68.7	4.4	10.8
						(67.8	4.4	10.7)
3k	C_6H_4-OCH_3(*p*)	C_6H_4-Cl(*o*)	232	50	$C_{30}H_{23}N_4O_4Cl$	66.9	4.3	10.3
						(66.8	4.2	10.4)
3l	C_6H_4-Cl(*o*)	C_6H_4-NO_2(*p*)	241	45	$C_{29}H_{20}N_5O_5Cl$	62.8	3.5	12.7
						(62.8	3.6	12.6)
4a	C_6H_5	--	170	70	$C_{30}H_{22}N_2O_3$	78.5	4.8	6.0
						(78.6	4.8	6.1)
4b	C_6H_4-Cl(*p*)	--	188	60	$C_{30}H_{21}N_2O_3Ci$	72.8	4.1	5.5
						(73.0	4.2	5.6)
4c	C_6H_4-Cl(*o*)	--	195	65	$C_{30}H_{21}N_2O_3Cl$	73.1	4.3	5.6
						(73.0	4.2	5.6)
4d	C_6H_4-OCH_3(*p*)	--	157	70	$C_{31}H_{24}N_2O_4$	76.1	4.9	5.6
						(76.2	4.5	5.7)
4e	C_6H_4-CH_3(*p*)	--	164	65	$C_{31}H_{24}N_2O_3$	78.9	4.9	5.8
						(78.8	5.0	5.9)

The PMR spectra (δ ppm) of 4a shows a doublet for two protons of C_9 and C_{10} at 4.8, and a doublet for maleimide ring protons of C_{11} and C_{15} at 3.4 (J = 4 Hz). The *endo* 4a and *exo* 4b structures were proposed on the assumption that the methine protons (C_{11} and C_{15}) which on the α-carbon to carbonyl and *anti* to the benzene ring in *exo* isomer 4b should be relatively more deshielded than the methine proton of the corresponding *endo* isomer 4a, in which the proton lie closer to the shelding region of the ring current (14). In these compounds, the methine protons of C_{11} and C_{15} are more shielded and appear at δ 3.4 which confirm *endo* isomer 4a. If these protons are not under the shielding region of ring current, they might have appeared in downfield region (the value is higher than δ 3.4, i.e., between δ 3.5 – 4.0) confirm that the product obtained possess *endo* structure rather than *exo* structure.

Experimental

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by chromatography over silica gel thin layers (silica gel-G). IR spectra were run as KBr pellets on a Perkin-Elmer spectrum BX series FT-IR spectrometer (ν_{max} in cm^{-1}) and ^1H NMR spectra were recorded in $CDCl_3$ on a 200 MHz Varian Gemini instrument with TMS as internal standard (chemical shifts in δ ppm). Mass spectra was run on a Jeol JMC D-300 spectrometer at 70 eV.

Preparation of 1-phenyl-3-aryl-5-*N*-(3-methyl-5-styryl-4-isoxazolyl)-4,6-dioxopyrrolo-[3,4-*d*]-7.8-dihydropyrazoles 3

A mixture of isoxazolyl maleimide (0.01 mole), in ethanol was added to a mixture of arylhydrazone (0.01 mole) and chloramine-T (0.02 mole) in ethanol and the contents refluxed for 4 hrs. Salts are filtered off, the filtrate was evaporated under vaccum and the residue is extracted into ether (25 ml). The ethereal layer is washed with IN sodium hydroxide (2 x 10 ml), brine solution (2 x 15 ml) and dried. Concentration of the solvent furnished crude product, which was crystallized from benzene-ethyl acetate to get colourless solid **3**.

Preparation of 9,10-dihydro-anthracene-9,10-*endo*-*N*-(3-methyl-5-styryl-4-isoxazolyl)-maleimides 4

A mixture of maleimide (0.01 mole), anthracene (0.01 mole) and aluminium chloride (0.01 mole) in dichloromethane (20 ml) is stirred for 15 minutes at room temperature. The mixture was poured into cold water and extracted with excess of dichloromethane. The organic layer was washed with water, concentrated by rotary evaporator and dried over Na_2SO_4. Recrystallization from benzene afforded white crystalline solid 4.

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Spectra of representative compounds

3a : IR (KBr) : 1600 (C=N), 1660 (C=O) cm^{-1};' ^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.4 (s, 3H, CH_3), 4.5 (d, 1H, C_4-*H*, *J* = 5 Hz), 4.7 (d, 1H, C_5-*H*, *J* = 5 Hz), 6.8 (d, 1H, -CH=CH-, J = 15 Hz), 7.0 (d, 1H, -CH=CH-, J = 15 Hz), 7.1-7.8 (m, 10, Ar-H); MS : m/z 474; **3c** : IR (KBr) : 1610 (C=N), 1670 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.3 (s, 3H, CH_3), 4.6 (d, 1H, C_4-*H*, *J* = 5 Hz), 4.8 (d, 1H, C_5-*H*, *J* = 5 Hz), 6.8 (d, 1H, -CH=CH-, *J* = 15 Hz), 7.0 (d, 1H, -CH=CH-, *J* = 15 Hz), 7.1-7.6 (m, 9H, Ar-H MS : m/z 508.

4a : IR (KBr) : 1680 (C=0), 2900 (C-H) cm^{-1};' ^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.3 (s, 3H, CH_3), 4.8 (d, 2H, C_9 & C_{10}-*H*), 3.4 (d, 2H, C_{11} & C_{15}-*H*), J = 5 Hz), 6.8 (d, 1H, CH=CH, J = 15 Hz). 7.10 (d, 1H, C=CH-, J = 15 Hz), 7.2-8.0 (m, 12H, Ar-H), MS : m/z 458; **4c** : IR (KBr) : 1675 (C=0), 2915 (C-H) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.4 (s, 3H, CH_3), 4.4 (d, 2H, C_9 & C_{10}-*H*), 3.8 (d, 2H, C_{11} & C_{15}-*H*, *J* = 5 Hz), 6.8 (d, 1H, HC=CH, J = 15 Hz), 7.0 (d, 1H, CH=CH, *J* = 15 Hz), 7.1-7.8 (m, 11H, Ar-H); MS : m/z 492.

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